

Pharmacological alternatives to Antipsychotics in the Management of BPSD

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Abstract

In this review, we will discuss the evidence and provide an update on the pharmacological treatments of Behavioural and Psychological symptoms of Dementia (BPSD) especially anti-psychotic medications. Non-pharmacological management of BPSD remains the initial treatment for BPSD; however, pharmacological management have a role in specific situations. This review should support the management of elderly inpatients suffering from Dementia and challenging behaviour in mental health units, general hospitals, community settings and care homes. It will help in raising awareness to the risk of complications such as stroke/death associated with first and second generation antipsychotic medications. It will also highlight some issues in relation to the current guidelines and licensing in the USA, UK and Europe. Good clinical practice used in the management of BPSD to reduce the risk of stroke and other complications is included.

What is BPSD?

Dementia is a progressive and largely irreversible clinical syndrome characterised by widespread impairment of mental function.¹ Behavioural and Psychological symptoms of Dementia (BPSD) is a term introduced in the 1990s,² with an estimated incidence of up to 75% of people with Dementia may be affected by non-cognitive symptoms and challenging behaviour.¹ Dementia patients can experience changes in personality, self-neglect, apathy, depression, aggression, restlessness, wandering and disruptive vocal activity, sleep disturbance, and disinhibited sexual behaviour. Table 1 summarises BPSD frequency depending on Alzheimer's disease (AD) stages; the domains were evaluated using the Neuro Psychiatric Inventory.

Table 1: Frequency of BPSD across AD stages

	Mild*	Moderate **	Severe*
Apathy	47%	67%	92%
Agitation	47%	45%	85%
Aberrant Motor	12%	53%	84%
Depression	12%	52%	62%
Anxiety	24%	49%	54%
Irritability	35%	35%	54%
Delusions	12%	37%	31%
Disinhibition	35%	22%	31%
Hallucinations	12%	24%	8%
Euphoria	18%	8%	8%

*³

**⁴

Apathy is a disorder of motivation that persists over time; its formal diagnosis requires the following criteria: Diminished motivation for at least four weeks, two of the three dimensions of apathy (reduced goal-directed behaviour, goal-directed cognitive activity and emotions). These symptoms result in functional impairment; not exclusively explained by physical disability or a substance effects.⁵

It appears that Depression, Apathy, Delusions, Anxiety and agitation are more frequent in severe compared to mild Dementia; while hallucinations less frequent in severe compared to moderate Dementia (Table 1).

Sexually disinhibited behaviours are common, with prevalence between 2-17%, with almost equal frequency in men and women.⁶ These may include explicit sexual comments, exposing the breasts or genitals in public, touching someone inappropriately; while some behaviour still ambiguous such as undressing outside the bathroom or bedroom. There is no widely agreed definition for an abnormal sexual behaviour in Dementia and is based on judging what is normal for a person in a particular situation. Accordingly, there is a difference based on the setting; for example if the patient is at home, a residential home or in hospital depending on the level of risk or discomfort on others.⁶

People suffering from BPSD should be offered an assessment at an early opportunity including physical health, depression, undetected pain, medication

adverse effects, psychosocial factors.¹ Individually tailored care plans should be developed, recorded in the notes and reviewed regularly.¹

Can certain drugs increase BPSD risk?

Medications with anticholinergic activities have a potential to cause symptoms of BPSD such as delirium and confusion. These medications include Tricyclic antidepressants, [first generation antipsychotics](#), urinary retention medications like oxybutynin, H2-antagonists such as cimetidine and antibiotics such as quinolones, anticonvulsants such as carbamazepine. Furthermore, some medications are known to be associated with side effects such as an increase the risk of depression with as B-blockers and anticonvulsants. Drugs causing Psychosis symptoms include systemic steroids, NSAIDS.⁷

Can the pharmacological management be the first response to BPSD?

Non-Pharmacological management should be the first response. However, pharmacological treatment may be an appropriate first response if there is a specific indication; for example; Psychosis or depression, severe symptoms, distressing to patients or others and treatment is urgently needed and the behaviour has no clear situational trigger or occurs in a setting where carers cannot cope.⁸ In addition, pharmacological treatment has a role if there is an immediate risk of harm to the patient or others.¹ There is a need for carers in care homes to have further Dementia training; for example a recent primary survey in the west Midlands on Perceptions about the levels of dementia

training among staff in dementia registered care homes identified that 19 % of staff that participated in the survey felt that further training is needed in Behavioral and Psychological symptoms of Dementia ⁵⁷

Antipsychotics used to treat BPSD are arbitrarily divided into typical (first generation) and atypical (second generation). Antipsychotics block [Dopamine \(DA\)](#) receptor in the mesolimbic, mesocortical and the therapeutic efficacy [is thought to](#) correlate with their affinity for D2-receptors, [although other mechanisms are likely to contribute.](#) The binding to the basal ganglia and pituitary glands D2-receptors lead to their [extensive](#) side effects.

Atypical antipsychotics such as olanzapine have a relatively low affinity for D2-receptors, which does not correlate with their clinically effective dose. They are 5-HT₂ and D₄-receptors antagonists with effectiveness in physical aggression, agitation and psychosis. ⁹⁻¹¹ There is a modest but significant effectiveness in treatment of aggression in AD. ¹²

On the other hand, there was concern regarding the safety of administering atypical antipsychotics to elderly as shown in the Committee on Safety of Medicines (CSM) alert on atypical antipsychotic use in BPSD patients. ¹³ This followed manufacturer data, which showed an increased risk of cerebrovascular adverse events ranging from transient ischemic attacks to strokes with [risperidone](#) and [olanzapine](#). The CSM suggested a three-fold increased risk of cardiovascular adverse effects from 1.1%-3.3% over 12-week period. In addition, [risperidone](#) is associated with additional risk of death when co-prescribed with furosemide. ¹⁴

The Faculty of Old Age Psychiatry issued guidance with the British Geriatrics Society, the Royal College of General Practitioners and the Alzheimer's Society on atypical antipsychotics use in BPSD patients.⁸ Since then, there were reports that patients had their medication inappropriately withdrawn or switched.⁸ Furthermore, there were pharmaceutical issues such as polypharmacy with the prescribing of several antipsychotics concurrently or medications administered at high doses even exceeding the BNF limits or medications given for too long without reviewing the need or the dose.¹⁵ The use of antipsychotics appears to be associated with accelerated cognitive decline in people with AD.¹⁶

Risk of death from prescribing antipsychotics

The Food and Drugs Administration (FDA) concluded that labelling for all atypical antipsychotics should include information regarding the increased risk of mortality in dementia. This was based on a meta-analysis of 17 placebo-controlled trials of four atypical antipsychotics. These trials showed the risk of death in the drug-treated patients was 1.6 to 1.7 times higher compared to placebo. The main causes of deaths appeared either cardiovascular or infections. Because of the results consistency, the FDA concluded that the effect is likely related to the common pharmacologic effects of atypical antipsychotics, including those not included in the meta-analysis.¹⁷

Around 180,000 dementia patients are treated with antipsychotics in the UK per year, up to 36,000 may benefit from the treatment. In terms of negative effects directly attributable to antipsychotics, use at this level equates to additional 1,800 deaths and 1,620 cerebrovascular adverse events. The

proportion of these prescriptions which would be unnecessary if appropriate support were available is unclear.¹⁸ There were significant changes in the management of BPSD using antipsychotics since the publication of the Banerjee report.

Are conventional antipsychotics safer?

Typical antipsychotics are relatively less effective at controlling schizophrenia negative symptoms. Two large observational and epidemiological studies examined the risk of death in patients on conventional antipsychotics. The first study included 27,259 subjects with a diagnosis of dementia and compared the risk for death with atypical antipsychotic versus no antipsychotic or conventional antipsychotic. Conventional antipsychotics use showed a marginally higher risk of death compared with atypical antipsychotics.¹⁹ Another study included 37,241 subjects, prescribed either conventional or atypical antipsychotics and demonstrated that the risk of death with conventional antipsychotics was comparable, and possibly greater than atypical antipsychotics.²⁰ Due to methodological limitations, FDA highlighted that these results preclude any conclusion that conventional antipsychotic medications have a greater risk of death. However, FDA determined that the overall weight of evidence indicated that conventional antipsychotics share the increased risk of death observed for atypical antipsychotics.²¹

FDA notified healthcare professionals that conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients and requires manufacturers to make safety-label changes (Table 2). FDA and NICE recommend physicians, who prescribe antipsychotics to

discuss the risk of increased mortality with their dementia patients, patients' families and caregivers.

Table 2: Drugs with safety-labels changes

Comment [AA1]: Table 2 has been removed due to the word limit and as suggested by the reviewer

Typical Antipsychotic Drugs	Atypical Antipsychotic Drugs
Prochlorperazine	Aripiprazole
Haloperidol	Clozapine
Loxapine	Ziprasidone (unlicensed in the UK)
Thioridazine	Paliperidone
Molindone	Risperidone
Thiothixene	Quetiapine
Pimozide	Olanzapine
Fluphenazine	
Trifluoperazine	
Chlorpromazine	-
Perphenazine	-

The Committee for Medicinal Products for Human Use concluded there is ample evidence that conventional antipsychotics are associated with an increase the risk of death in dementia.²² European Medicines Agency highlighted in addition to the FDA evidence that ten further publications showed the risk of death associated with conventional antipsychotics. Seven of them concluded that conventional antipsychotics are associated with

increased mortality, whilst three concluded that neither atypical nor conventional antipsychotics are associated with increased mortality.²²

Licensing and Guidelines in the UK:

In the UK, there is no drug currently licensed specifically for BPSD management.⁸ Risperidone is licensed for short term treatment (up to six weeks) of persistent aggression in moderate to severe AD unresponsive to non-pharmacological interventions and when there is a risk to harm.²³ This appears to contradict with the evidence that antipsychotics are associated with increased risk of stroke as early as thirty days of treatment.¹⁹

Anti-Dementia drugs licensed for cognition treatment not behaviour; cholinesterase inhibitors are licensed for mild to moderate AD, rivastigmine for mild to moderate [Parkinson's Disease Dementia \(PDD\)](#).²⁴ The only drug currently used for severe AD is memantine.¹ Donepezil inhibits acetylcholinesterase with side effects such as cardiac arrhythmia; gastrointestinal disturbances; pancreatitis, stroke, seizure, delirium, vivid dreams, insomnia. Memantine is a non-competitive NMDA antagonist as excessive glutamate excitotoxicity is implicated in dementia.

What evidence supports use of Pharmacological alternatives?

Anti-dementia medications may have a beneficial effect on some behavioural symptoms.²⁵⁻²⁷ Cholinesterase inhibitors efficacy was demonstrated in several large RCTs²⁶⁻²⁸ as they reduce psychotic symptoms in dementia and can be a good alternative to antipsychotics.

Current guidelines state AD patients with non-cognitive symptoms and/or challenging behaviour may be offered cholinesterase inhibitor if non-pharmacological approach and antipsychotics were inappropriate or ineffective.¹ However, for vascular dementia patients, the current guidelines do not recommend these medications except as part of clinical studies.¹

The Faculty of Old Age Psychiatry health technology appraisal recognised the adverse-effects associated with antipsychotics and highlighted the benefits of cholinesterase inhibitors and memantine. It urged NICE to ensure these medications are not so restricted leading clinicians to consider the use of antipsychotics. The faculty suggested memantine should be recommended as a treatment option for patients with moderate to severe AD where there are prominent behavioural symptoms not managed by non-pharmacological means and when alternative therapeutic options would involve high risk.⁸

In NICE guidance, cholinesterase inhibitors are options for managing mild and moderate AD, while memantine for moderate AD people who cannot take cholinesterase inhibitors and severe AD.¹ Patients on memantine were slightly less likely to develop agitation (12% vs 18% in the control group).²⁹

Anticonvulsants:

Limited evidence suggests lamotrigine may be helpful for agitation and psychosis in dementia.³⁰ Lamotrigine is an antiepileptic whose mechanism of action is linked to voltage-sensitive sodium-channel blockade in the neuronal membrane and inhibition of glutamate and aspartate release.³¹ Lamotrigine has good concordance, acceptable side-effects margin, however a rash on

initiation can influence adherence/continuation, and no worsening in the cognitive functions.³¹ Large clinical trials are required to confirm Lamotrigine positive clinical outcome. Carbamazepine acts on sodium-channels with demonstrated efficacy in agitation treatment.³² Gabapentin, a structural analogue of GABA, has shown efficacy in the management of behavioural symptoms in AD.^{33, 34} There is no enough evidence to support the use of valproic acid in the management of BPSD and even suggest that caution is needed.³⁵

Selective Serotonin Reuptake Inhibitors (SSRI)

SSRI are the first line in depression treatment, include fluoxetine, citalopram, escitalopram, paroxetine, and sertraline. SSRIs possess a relative advantageous safety profile with similar efficacy to TCAs; they inhibit serotonin reuptake through 5-HT transporters; SSRIs lack significant cardiotoxicity (except citalopram) with less anti-muscarinic, anti-adrenergic properties. Citalopram has shown efficacy in AD patients in reducing agitation and caregiver distress in combination with psychosocial intervention.³⁶ However, efficacy in treating depression in dementia is not fully supported.³⁷

SSRIs can cause sexual dysfunction, GI distress, bleeding complications and rarely serotonin syndrome. Serotonergic deficits in AD contribute to verbal and physical aggression, sleep disturbance, depression and psychosis.³⁸ Common 5-HT receptor polymorphisms have been associated with visual hallucinations in AD;³⁹ aggression and psychosis in AD were associated with 5-HT transporters polymorphisms.⁴⁰

Psychotic symptoms in AD are distinct from schizophrenia; 61% of patients experiencing hallucinations had only visual hallucinations.⁴¹ Delusions in dementia may result from misperceptions and impaired judgment. Consequently, delusions in AD may be attenuated by SSRI anxiolytic effect.⁴² Citalopram was efficacious in the short-term treatment of BPSD in dementia.⁴³ European Data from different countries including Switzerland, Germany and Austria suggested SSRI a first-line in about 30% of BPSD patients.⁴⁴

Trazodone blocks 5-HT_{2A} and 5-HT_{2C} receptors and inhibits serotonin transporter, showed efficacy in controlling BPSD (a randomised controlled trial, a case series and other smaller studies),^{45, 46} however another study suggested that its efficacy was similar to placebo.⁴⁷

Pharmacological Treatment of Sexually disinhibited behaviours

There are no drugs currently licensed in the UK for sexually disinhibited behaviours; neuroleptics, anti-androgens, oestrogens, LHRH analogues, ~~Serotonergics~~serotonergics, ~~Gabapentin~~gabapentin are occasionally used off-license.⁶ There is a scarce evidence for Neuroleptics. Citalopram and paroxetine, with a relatively safe profile, are associated with improvement in sexual aggression and disinhibition.⁴⁸ Clomipramine, a TCA that inhibits serotonin and noradrenaline reuptake, was effective.⁴⁹ However, there are issues that need reviewing before recommending clomipramine as there is increased risk of falls and worsening confusion.

Cimetidine, a H2-antagonist was associated with a reduction in libido and hypersexual behaviour in 14 out of 20 patients without remarkable side-effects. The other patients responded to combinations of cimetidine with ketoconazole, spironolactone; however the safety profile of using these combinations should be appropriately reviewed.⁵⁰

Gabapentin showed a reduction in agitation and inappropriate sexual behaviour in vascular Dementia⁵¹ and AD.⁵²

Little is known about oestrogens and LHRH analogues; and there are no controlled studies for anti-androgens for the treatment of sexual disinhibition in dementia⁵³ but they were used in sexual offenders.⁶ There are few reports on oestrogens for treating hypersexuality associated with dementia, however more robust evidence is needed, and especially that oestrogen use is associated with cardiovascular-related deaths.⁵³

Discussion:

Early Data in a survey for Old Age psychiatrists showed that most of the respondents (95.5%) disagreed with the statement that antipsychotics should never be prescribed for patients with dementia and all reported that they prescribed antipsychotics for BPSD management.⁵⁴

In light of the risk of death with conventional and atypical antipsychotics and their financial implications, antipsychotic medications should be avoided. This may apply after failure of non-pharmacological methods to manage BPSD, provided that there is evidence for safer pharmacological alternatives. However more robust studies are needed to validate the effectiveness and

safety of the alternatives medications especially that they appear to be cost-effective. There are challenges in the assessment and treatment of patients with Behavioural and Psychological symptoms of Dementia and consequently a tailored care plan will be needed for each patient based on a person centred approach and especially depending on an identifiable symptom that needs to be treated.

Withdrawal of antipsychotics improves functional and cognitive status in AD patients and can be achieved successfully in people relatively free from behavioural symptoms for at least 3 months.⁵⁵ However, it is prudent to withdraw antipsychotics cautiously and gradually except for specific and distressing medications side-effects. On the other hand, not everyone on atypical antipsychotics should have their drug stopped or changed as BPSD can persist in the long-term and often resistant to treatment. Atypical antipsychotics can be continued if severe adverse consequences may occur (or have occurred) if the medications are discontinued or when no alternative treatment approaches suitable.

Is there a need for local protocols for the management of BPSD?

There is conflicting information from different sources such as academic literature, Pharmaceutical industry, guidelines, Health Trusts policies, local experts and licensing authorities regarding the appropriate management of BPSD using pharmacological treatments.

National Guidelines are expected to be influential and safe. Evidence-based approach sees the bigger picture and is politically neutral with less risk of bias, but is time consuming. Local expert opinion can vary widely and may be influenced by local pharmaceutical exposure and is considered not cost-effective with protocols for prescribing, monitoring need to be introduced. Some hospitals developed local protocols with algorithms and flow charts suggesting first and second lines in BPSD pharmacological treatment.

Algorithms use graphic representation for a logical scientific approach to a clinical problem. If wisely administered, algorithms have a role in patients-care and cost-effectiveness. However a valid criticism centres on its rigidity and the automatic approach that fosters within the clinical field, by neglecting individual factors, especially when such algorithms are poorly applied.⁵⁶ The guidelines do not override healthcare professionals' responsibility to make appropriate decisions depending on the patients' circumstances, in consultation with the patient and/or their carer.¹

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